Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Data Collection and Case Report Form (CRF)

The standardized case report form utilized for inpatient and outpatient data collection for the prospective cohorts in Melbourne (Austin Health and Peter MacCallum Cancer Centre) are provided in the following.

In brief, this standardized case report form was completed by the treating clinician (including trained infectious diseases physicians) during inpatient or outpatient consultation. Allergy phenotypic assessment was at clinician discretion utilizing patient-reported phenotypes and standard definitions for anaphylaxis[8] and potential severe cutaneous adverse reactions (SCAR - DRESS[9]; SJS/TEN[10]; AGEP[11]), as performed in previous publications utilizing this dataset.[1,12]

In brief, anaphylaxis was adjudged by the clinician if the history was consistent with a cutaneous manifestation plus one of respiratory, cardiovascular or gastrointestinal symptoms or acute onset hypotension or bronchospasm/airway obstruction alone. SJS/TEN also included potentially compatible syndromes of rash with mucosal ulceration.

Every attempt was made to reconcile the patient-reported label (e.g. “anaphylaxis”) with a detailed history of the allergy event from the patient supplemented with hospital medical records but where this was not available, the patient-reported label was used.

FORM 01

ANTIBIOTIC ALLERGY CLINIC

DATA COLLECTION FORM

1- Baseline Demographic:

UR number: _____ Cohort ID: _____ (*office use*)

Site: ❑ Austin ❑ PMCC ❑ Vanderbilt

Age: _____ Sex: ❑ male ❑ female ❑ transsexual

Ethnicity: ❑ African ❑ Asian ❑ Caucasian

COB: _____

Referrer: (*multiple choices*) ☐ LMO ☐ ADR committee ☐ community specialist ☐ allergist ☐ pharmacist ☐ ID physician ☐ respiratory physician ☐ other doctor

First Clinical Review Date: _____/_____/ 20 _____ (*1st antibiotic allergy clinic appointment*)

First Allergy Test Date: _____/_____/ 20 _____ or ☐ not done

Psychiatric history: ☐ no ☐ unk
☐ anxiety ☐ bipolar ☐ depression
☐ personality disorder ☐ psychosis

Age adjust CCI (*refer to **Charlson comorbidity index***): _____

Antibiotics previously tolerated (*list them all*):_____

_____

2- Immunosuppression history:

Immunosuppressed: ☐ no→*go to **section 3, "Family History"***

☐ Autoimmune ☐ Connective tissue disorder

☐ Haematological Malignancy ☐ Oncological Malignancy

☐ Diabetes (insulin requiring) ☐ Inflammatory Bowel Disease

☐ Prednisolone > 10mg/day for month ☐ Rheumatological disorder

☐ Allogeneic transplant ☐ Autologoustransplant

☐ Lung transplant ☐ Liver transplant

☐ Renal transplant ☐ Renal/ pancreas transplant

☐ Other

Transplant: ☐ no
☐ yes → days post last transplant: _____

Transplant rejection: ☐ no
☐ yes → episode/s requiring treatment: _____

Immunosuppressed at first clinical review: ☐ no
☐ yes → *tick as many as apply*

❑ AML induct/consol ❑ azacitidine ❑ azathioprine ❑ chemotherapy

❑ cyclosporin ❑ everolimus ❑ ibrutinib ❑ MMF

❑ myeloma ❑ methotrexate ❑ rituximab ❑ sirolimus

❑ small molecule inhibitor (solid tumours) ❑ tacrolimus ❑ TNF inhibitor

❑ other

Prednisolone: ☐ no ☐ yes → Daily dose (mg): _____

3- Family Allergy History:

Allergy history: ☐ no → *go to* ***section 4***
☐ yes

Antibiotic allergy history: ❑ no ❑ yes

Drug allergy history: ❑ no ❑ yes

Food allergy history: ❑ no ❑ yes

Environmental allergy history: ❑ no ❑ yes

4- Radioallergosorbent test

RAST performed: ☐ no ☐ yes → ❑ neg
❑ pos→against: ♦amoxycillin (*circle*) no / yes
♦cefaclor: (*circle*) no / yes
♦penicillin: (*circle*) no / yes

Neutropenia: ☐ no ☐ yes

Neutropenia < 0.5: ☐ no ☐ yes

Anaemia <10: ☐ no ☐ yes

Total lymphocyte count: _____ Date: _____/_____/ 20_____

CD4 count: _____ Date: _____/_____/ 20_____

CD4 %: _____ Date: _____/_____/ 20 _____

IgG total: _____ Date: _____/_____/ 20_____

IgA total: _____ Date: _____/_____/ 20_____

FORM 01

5- Antibiotic Allergy History:

☐ no → **END of study**

☐ yes →Time since last antibiotic allergy or Adverse drug event: _____ ***days***

Number of allergy labels: _____ →**list All** *(refer to* **FORM 02** ***section 6, Antibiotic Allergy Label****)*

Previous SPT/IDT test: ☐ no
☐ yes → ❑ neg
❑ pos → *tick all agents that apply*

Agent:				
	❍ ampicillin	❍ aztreonam	❍ azithromycin	❍ bactrim
	❍ cefepime	❍ ceftazadim	❍ ceftriaxone	❍ cephazolin
	❍ ciprofloxacin	❍ clavulanic acid	❍ clindamycin	❍ DAP major
	❍ DAP minor	❍ flucloxacillin	❍ histamine	❍ meropenem
	❍ moxifloxacin	❍ penicillin	❍ penicillin G 1000	❍ penicillin G 10000
	❍ tazocin	❍ timentin	❍ vancomycin	

Would you be happy to be re-challenged with the offending antibiotic if negative on SPT/IDT testing?

☐ no → *go to* ***section 7*** ☐ yes

If the oral challenge allergy testing was negative, would you be willing to take that antibiotic in the future?

☐ no ☐ yes

7- Allergy Test Results:

Skin prick test performed: ☐ no ☐ yes → ❑ neg
❑ pos → *tick as many as apply*

Agent:				
	❍ ampicillin	❍ aztreonam	❍ azithromycin	❍ bactrim
	❍ cefepime	❍ ceftazadim	❍ ceftriaxone	❍ cephazolin
	❍ ciprofloxacin	❍ clavulanic acid	❍ clindamycin	❍ DAP major
	❍ DAP minor	❍ flucloxacillin	❍ histamine	❍ meropenem
	❍ moxifloxacin	❍ penicillin	❍ penicillin G 1000	❍ penicillin G 10000
	❍ tazocin	❍ timentin	❍ vancomycin	

Intradermal test: ☐ no ☐ yes → ❑ neg
❑ pos → *tick as many as apply*

Agent:				
	❍ ampicillin	❍ aztreonam	❍ azithromycin	❍ bactrim
	❍ cefepime	❍ ceftazadim	❍ ceftriaxone	❍ cephazolin

❍ ciprofloxacin ❍ clavulanic acid ❍ clindamycin ❍ DAP major

❍ DAP minor ❍ flucloxacillin ❍ histamine ❍ meropenem

❍ moxifloxacin ❍ penicillin ❍ penicillin G 1000 ❍ penicillin G 10000

❍ tazocin ❍ timentin ❍ vancomycin

Patch test: ☐ no ☐ yes → ❑ neg
❑ pos → *tick as many as apply*

Agent: ❍ Antiretroviral (other) ❍ Beta-lactam (other) ❍ Sulfamethoxazole

❍ Teicoplanin ❍ Trimethroprim ❍ Vancomycin

Direct oral challenge: ☐ no
☐ yes → *tick as many as apply*

❍ amoxycillin(S) ❍ amoxycillin (L) ❍ augmentin(S) ❍ augmentin(L)

❍ ciprofloxacin(S) ❍ ciprofloxacin(L) ❍ cephalexin(S) ❍ cephalexin(L)

❍ flucloxacillin ❍ penicillin(S) ❍ penicillin(L) ❍ tazocin

→post testing oral challenge: ❑ neg
❑ pos → *tick as many as apply*

◇ amoxycillin(S) ◇ amoxycillin(L) ◇ augmentin(S) ◇ augmentin(L)

◇ ciprofloxacin(S) ◇ ciprofloxacin(L) ◇ cephalexin(S) ◇ cephalexin(L)

◇ flucloxacillin ◇ penicillin(S) ◇ penicillin(L) ◇ tazocin

8- Antibiotic Allergy Label Post Testing:

De-labelled: ☐ no

☐ yes → how many _____

Revised label: ☐ no ☐ yes

Antibiotic label/s: _____

_____

Antibiotic label/s_30 days: _____

Antibiotic label/s_90 days: _____

Antibiotic label/s_365 days: _____

9- Antibiotic Usage and Admission (*refer to* FORM 03, ***section 9***)

Antibiotic usage and admission with infective diagnosis 60 days **prior** to testing:

☐ no ☐ yes → *go to **FORM 03** - section 9, **page 1***

Antibiotic usage and admission with infective diagnosis 12 months **prior** to testing:

☐ no ☐ yes → *go to **FORM 03** - section 9 , **page 2***

Antibiotic usage and admission with infective diagnosis 60 days **post** to testing:

☐ no ☐ yes → *go to **FORM 03** - section 9, **page 3***

Antibiotic usage and admission with infective diagnosis 12 months **post** to testing:

☐ no ☐ yes → *go to **FORM 03** - section 9, **page 4***

10- T-cell ELISpot

Referred for T-cell ELISpot: ☐ no

☐ yes → Blood taken _____ mLs

Date _____/_____/ 20_____

PBMC count _____

Result: ❑ neg

❑ pos → *list antibiotic/s*

_____

_____

_____

Referred for TCK analysis: ☐ no ☐ yes

Referred for HLA typing: ☐ no ☐ yes

FORM 02: Antibiotic Allergy Label

Section 6: (*make copy of this page for more allergy labels if necessary*)

Label number: _____ **Antibiotic name**: _____

Date started: _____/_____/ 20_____ Date stopped: _____/_____/ 20_____

Number of allergy episodes: _____ Date of reaction: _____/_____/ 20_____

Description: *tick all that apply*

☐Acute interstitial nephritis (urinalysis or Bx proven)		☐AGEP
☐Anaphylaxis		☐Angioedema
☐Collapse (unspecified)		☐Diffuse itch rash (nil other)
☐Diffuse non-itchy rash (nil other)		☐DRESS
☐Drug fever (nil other)		☐EM
☐FDE		☐Haematological disorder
☐Headache or dizziness	☐Itch (unspecified)	☐Localised rash (nil other)
☐Linear IgA		☐Liver failure (not specified)
☐Liver function derangement		☐N/V/D
☐Psychiatric		☐Rash/fever / lymphadenopathy
☐Rash with skin ulceration or blisters (unspecified)		☐Renal failure (not specified)
☐Respiratory distress	☐Seizures	☐Swelling (unspecified)
☐SJS/TENS overlap	☐SJS	☐TENS
☐Urticaria	☐other	☐unknown

Type: ☐ A ☐ B1 ☐ B2
☐ B3 ☐ B4 ☐ unk

Biopsy proven: ☐ no ☐ yes

Re-challenge: ☐ no

☐ yes →Adverse Event: ❑ no ❑ yes

Concurrent viral infection: ☐ no

☐ yes →*tick all that apply* ❑ CMV ❑ EBV

❑ HHV6 ❑ HHV8

❑ mycoplasma

❑ other respiratory virus

Concurrent neuroleptic agents: ☐ no

☐ yes

FORM 02: Antibiotic Allergy Label

☐ unk

Concurrent anti-inflammatory agents ☐ no

☐ yes

☐ unk

Concurrent antibiotics: ☐ no

☐ yes

Treatment: ☐ no

☐ yes →*tick all that apply:*

❑ prednisolone (*including dose*) _____ *mg*

❑ antihistamine ❑ adrenaline

❑ intragam ❑ surgery

Hospitalisation: ☐ no ☐ yes

ICU: ☐ no ☐ yes

Review by ID physician: ☐ no ☐ yes

Review by Allergist/Immunologist: ☐ no ☐ yes

eMethods 2. Antibiotic Allergy Testing (AAT) Procedures From Derivation and Validation Cohorts

Derivation and Internal Validation Cohorts – Melbourne (Australia)

AAT was performed for out- and in-patients as previously described for immediate and delayed hypersensitivities. [1,2] In brief, in all patients reporting a penicillin allergy, skin testing using the validated Diater (DAP; Madrid, Spain) was used for the major (benzylpenicilloyl-poyl-L-lysine [PPL]) [3] and minor determinant mixtures (MDM) in patients with a penicillin hypersensitivity[4], in addition to penicillin G (SPT 10,000 U/mL; IDT 1000 IU/mL and 10,000 IU/mL), ampicillin (25 mg/mL), flucloxacillin (2 mg/mL), cefazolin (1 mg/mL) and ceftriaxone (2.5 mg/mL) as per previously published protocols.[1,5] Following AAT, an observed oral penicillin challenge was undertaken (immediate hypersensitivity - single or two-step penicillin VK 250 mg or amoxicillin 250 mg]; delayed hypersensitivity - prolonged 5-day). For patients with a potential SCAR phenotype, testing was performed as per previously published methods[2], using the same panel of IDT reagents/concentrations as above –(isolated PT only performed in SJS/TEN). From April 2017, patients identified as having a pre-defined low risk criteria (i.e. childhood exanthema, delayed rash > 10 years previously, or Type A adverse drug reaction) as per a validated antibiotic allergy assessment tool were offered a direct oral penicillin VK 250 mg or amoxicillin 250 mg challenge without preceding skin testing.

External Validation Cohorts – Sydney (Australia), Perth (Australia), Nashville (USA)

Perth – A standard testing protocol for all patients reporting a penicillin allergy of Diater-DAP PPL (benzylpenicilloyl poly-L-lysine; 0.04 mg/mL) and MDM (sodium benzylpenicillin, benzylpenicilloic acid, sodium benzylpenicilloate; 1.5 mg/mL), penicillin G (SPT 10,000 IU/mL; IDT 1000 IU/mL and 10,000 IU/mL), amoxicillin (20 mg/mL), cefazolin (1 mg/mL), and ceftriaxone (1 mg/mL).

Sydney - Standard testing protocol of penicillin G (10,000 IU/mL) and amoxicillin (20 mg/mL). In moderate to high risk patients, Diater-DAP PPL (benzylpenicilloyl poly-L-lysine; 0.04 mg/mL), MDM (sodium benzylpenicillin, benzylpenicilloic acid, sodium benzylpenicilloate; 1.5 mg/mL), cefazolin (20mg/mL), and ceftriaxone (10mg/mL) were also tested.

Nashville - A standard protocol similar to that employed in the validation cohort from Melbourne (Australia), [1,5] consisting of Pre Pen[6], minor determinant mix (consisting of the alkalinization of Penicillin G)[7], ampicillin (25 mg/mL), penicillin G (1000 IU/mL and 10,000 IU/mL), cefazolin (1 mg/mL), and ceftriaxone (2.5 mg/mL).

Definitions of positive AAT results

In all cohorts (internal derivation/validation and external validation) a SPT considered positive in the setting of a wheal 3 mm more than control wheal and flare 5 mm more than control flare, read after 15 minutes. An IDT was considered positive if there was a 3 mm or greater increase in inoculation site (0.02 mL) with >5 mm flare, read after 15 minutes. A positive oral challenge excluded non-immune mediated reactions and only included patients reporting an immune-mediated reaction (e.g. rash), including those that reported delayed reactions captured by study centre.

eMethods 3. LASSO Logistic Regression With Cross-Validation

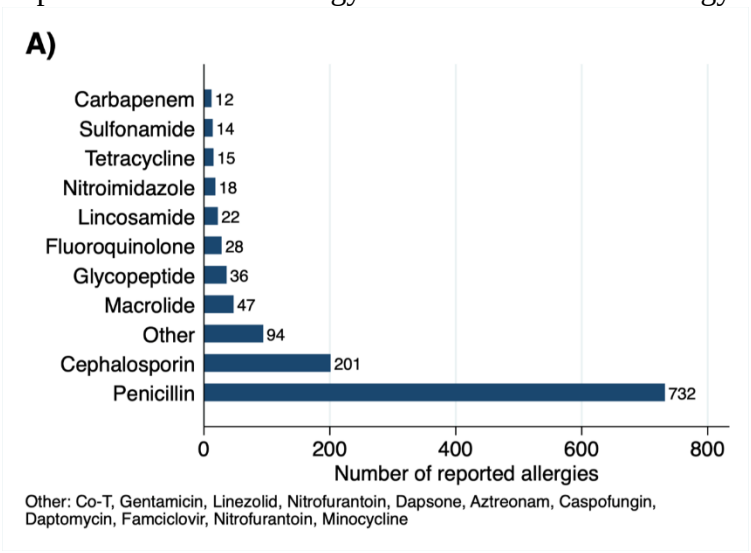
Logistic LASSO regression was also fitted using the same variables as stepwise logistic regression (main Table 3). Cross validation was used to select lambda (10-fold cross validation with 100 lambdas).

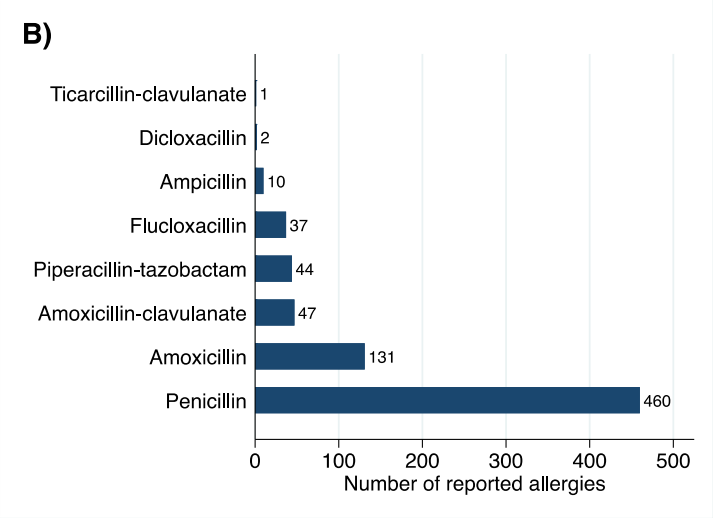
Final model consisted of 4 non-zero coefficient with lambda 0.016, and out-of-sample deviance ratio of 0.161. Variables with non-zero coefficients were the same as with the stepwise logistic regression with an additional variable of previous hospitalizations due to allergy. Penalized coefficients and coefficients from the logit model are presented in table.

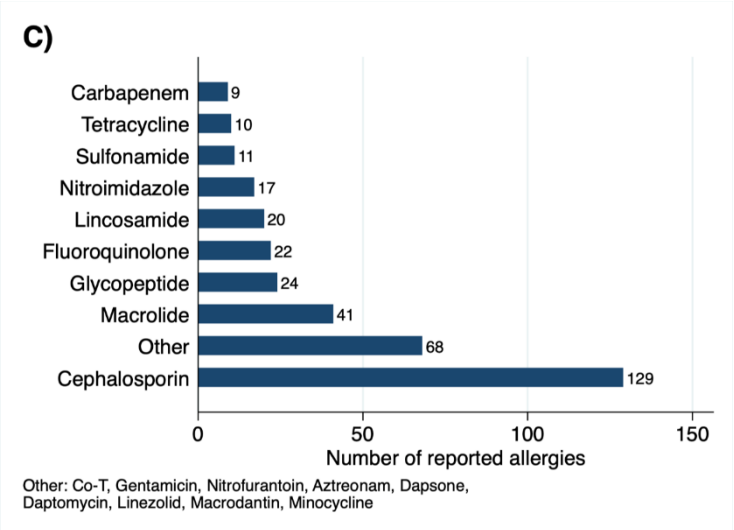
	LASSO logistic regression	Logit model	Stepwise logit model used in PEN-FAST
<5 years since last allergy or unknown	1.38	1.73	1.79
Anaphylaxis, angioedema, SJS, TENS, DRESS or AGEP	1.24	1.45	1.56
Treatment required†	0.33	0.88	1.02
Hospitalisation required	0.22	0.41	Not included
AUC of the model	0.817	0.817	0.808

† Any systemic treated as outlined in case report form (i.e. antihistamine, adrenaline, steroids, intragam)

eFigure 1. Patient-Reported Antibiotic Allergy Labels in Antibiotic Allergy–Tested Cohort

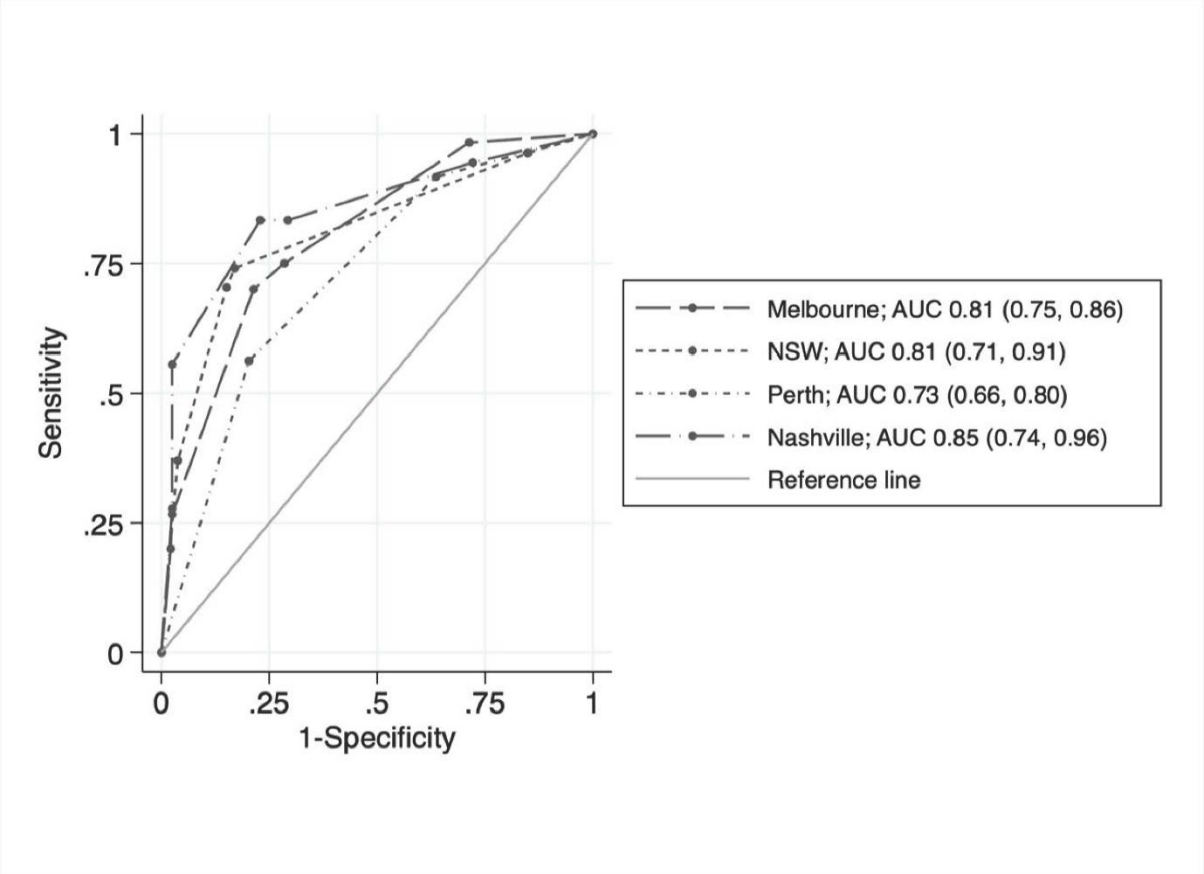






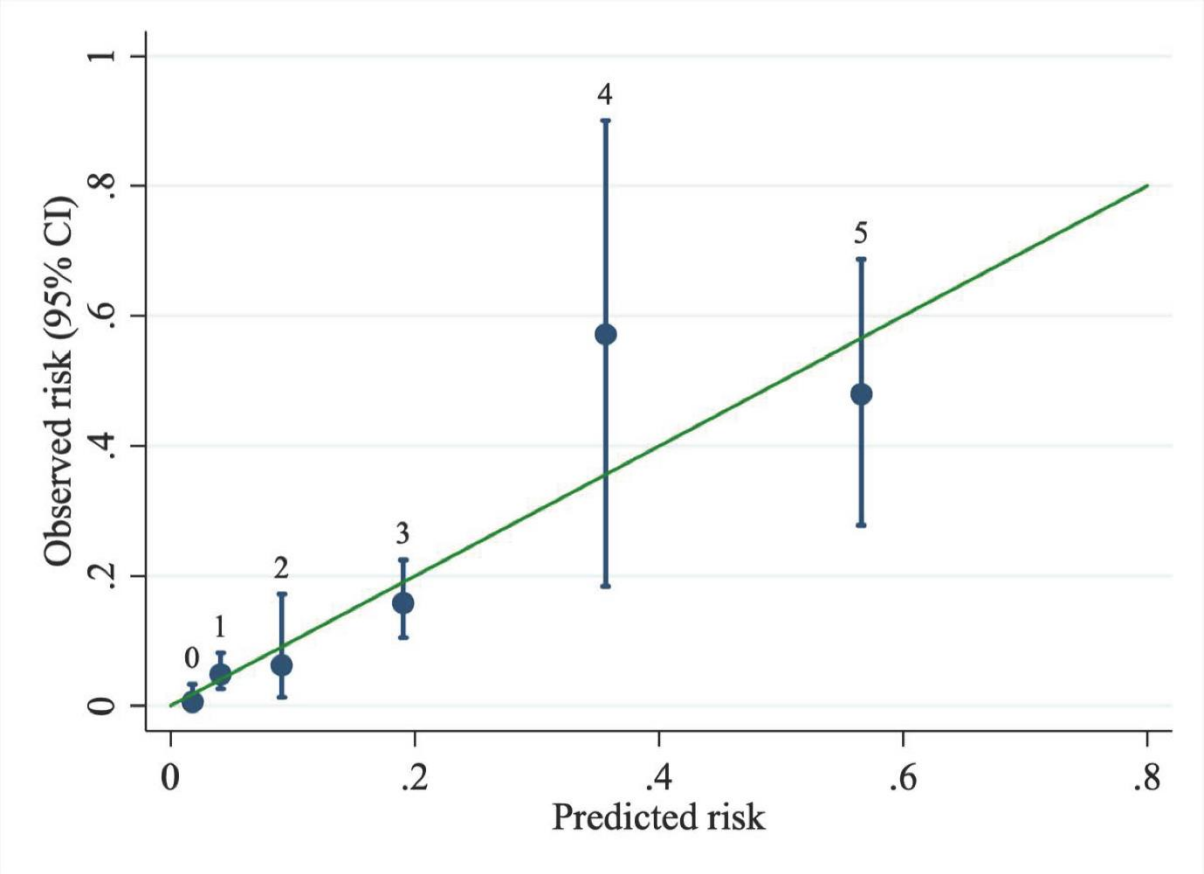
eFigure 1 Legend: (A) Antibiotic allergy labels recorded for all patients (n = 773) reporting an antibiotic allergy; (B) Penicillin allergy labels recorded for all patients (n = 679) reporting any penicillin allergy; (C) Non-penicillin allergy labels recorded for all patients (n = 679) reporting a penicillin allergy

eFigure 2. Area Under the Receiver Operating Characteristic Curve (AUC) Analysis



eFigure 2 Legend: AUC for PEN-FAST in the derivation/validation (Melbourne, Australia) and external validation cohorts (Sydney, Perth, Nashville).

eFigure 3. Calibration of the PEN-FAST Rule in Derivation/Validation Cohort (Melbourne, Australia)



eFigure 3 Legend: Numbers above the bars represent the PEN-FAST score

eTable 1. Baseline Demographics of External Validation Cohorts of Patients Reporting Any Oral Penicillin Allergy Who Underwent Testing as per Specified Methods

Patient characteristics	Perth (n = 334) No. (%)	Sydney (n = 80) No. (%)	Vanderbilt (n = 531) No. (%)
Age (years), median (IQR)	47 (31, 63)	52 (37, 63.5)	60 (44, 70)
Sex (female)	216 (64.7)	53 (66)	393 (74)
Allergy phenotypes			
Immune mediated			
SCAR	0 (0)	0 (0)	8 (1.6)
Angioedema/Anaphylaxis	130 (38.9)	17 (21.3)	112 (21.1)
Other†	201 (60.0)	45 (56.3)	399 (75)
Non-immune mediated	0 (0)	11 (13.8)	6 (1)
Unknown	3 (1)	7 (8.8)	6 (1)
Treatment for allergy‡			
Yes	0 (0)	26 (32.5)	161 (30.3)
No	0 (0)	43 (53.8)	220 (41.4)
Unknown	334 (100)	11 (13.8)	150 (28.2)
Time from reaction			
< 5 years	63 (19)	24 (30.0)	292 (55)
Skin prick and intradermal testing	332 (99.4)	78 (97.5)	531 (100)
Oral challenge	297 (88.9)	64 (80.0)	525 (98.9)
Any penicillin allergy test positive	48 (14)	27 (33.8)	19 (3.6)
IDT	42 (13)	17 (21.3)	15 (2.8)
Oral challenge	6 (3)	11 (13.8)	4 (1.7)

Abbreviations: SCAR, severe cutaneous adverse reaction; IQR, interquartile range; IDT, intradermal testing.
† Immune mediated reactions including rash (immediate or delayed), pruritis, respiratory or airway involvement.

‡ Any systemic therapy (i.e. antihistamine, adrenaline, steroids, intragam

eTable 2. Percentage of PEN-FAST Risk Scores for All Datasets Utilized

Clinical characteristics		Melbourne (AUS)	Sydney (AUS)	Perth (AUS)	Nashville (USA)
No. of patients		622	80	334	531
No. (%) of PEN-FAST risk scores					
	Very low risk (0)	164 (26)	9 (11.3)	0 (0)	79 (14.9)
	Low risk (1-2)	296 (48)	44 (55.0)	120 (35.9)	232 (43.7)
	Moderate risk (3)	132 (21)	15 (18.8)	140 (41.9)	147 (27.7)
	High risk (4-5)	30 (5)	12 (15)	74 (22.2)	73 (13.8)
No. (%) of allergy within PEN-FAST categories – observed risk					
	Very low risk (0)	1 (0.6)	1 (11.1)	n/a	1 (1.3)
	Low risk (1-2)	16 (5.4)	7 (15.9)	6 (5.0)	4 (1.7)
	Moderate risk (3)	25 (18.9)	9 (60.0)	15 (10.7)	5 (3.4)
	High risk (4-5)	16 (53.3)	10 (83.3)	27 (36.5)	9 (12.3)

Abbreviations: No., number

eTable 3. Derivation of Cutoff Scores for Clinical Decision Rule, PEN-FAST

Score	Negative CDR	False negative score†	Positive CDR	False positive score‡	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC (95% CI)
≥1	164 (26.4%)	1 (0.6%)	458 (73.6%)	401 (87.6%)	98.3 (90.8,100.0)	28.9 (25.2,32.8)	12.4 (9.6,15.8)	99.4 (96.6,100.0)	0.64 (0.61,0.66)
≥2	417 (67.0%)	14 (3.4%)	205 (33.0%)	161 (78.5%)	75.9 (62.8, 86.1)	71.5 (67.5,75.1)	21.5 (16.0,27.7)	96.6 (94.4,98.2)	0.74 (0.68,0.80)
≥3	**460 (74.0%)**	**17 (3.7%)**	**162 (26.0%)**	**121 (74.7%)**	**70.7 (57.3, 81.9)**	**78.5 (74.9,81.9)**	**25.3 (18.8,32.7)**	**96.3 (94.1,97.8)**	**0.75 (0.68,0.81)**
≥4	592 (95.2%)	42 (7.1%)	30 (4.8%)	14 (46.7%)	27.6 (16.7, 40.9)	97.5 (95.9,98.6)	53.3 (34.3,71.7)	92.9 (90.5, 94.8)	0.63 (0.57,0.68)

Abbreviations: CDR, clinical decision rule; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under receiver-operator curve.
† Positive penicillin allergy test (any)
‡ Negative penicillin allergy test (any)

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